2. STUDY REPORT SYNOPSIS OF PROTOCOL 7164-L-01

Name of Sponsor Company **Zambon Group S.p.A.**	*Individual Study Table referring to the dossier* PART: [……] VOLUME: [……] PAGE: [……]	*(for National Authority use only)*
Name of finished product		
Name of active ingredient **Pholcodine**		

Title of the study

A MULTICENTER, RANDOMIZED, PARALLEL GROUP, CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF PHOLCODINE AS ANTITUSSIVE AGENT VS DEXTROMETORPHAN IN NON-PRODUCTIVE COUGH

Principal Investigators and study sites

The study took place in Italy and involved 20 recruiters General Practitioners.

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Publication (reference)	*Clinical phase*
Unpublished (2005)	Phase 3
Date of first enrolment	***Date of last completed***
7 March 2005 (1st patient randomized)	17 June 2005 (last patient, last visit)

Objectives

Primary Objective

To show that a 3-day treatment with pholcodine exhibits comparable efficacy, in terms of daytime cough frequency versus DXM in patients with acute non-productive cough.

Secondary Objectives

(a) To compare the efficacy of the treatment with pholcodine versus DXM treatment in terms of cough intensity.
(b) To compare the efficacy of a treatment with pholcodine versus DXM treatment in terms of night time symptoms.
(c) To compare the safety of a treatment with pholcodine versus DXM treatment in terms of incidence of adverse events.
(d) To evaluate the global efficacy and tolerability of treatment with pholcodine.

Study design

Multicenter, national, prospective, double-blind, randomized, active-controlled, parallel-group study. Patients were to be screened and randomized to either pholcodine or dextrometorphan treatment on the same day. Each patient was maintained in the study for a maximum of 7 days (day 0 for inclusion, 3 days of treatment, with follow-up visit within 3 days from the last administration).

Patient population

About 150 patients were planned to be enrolled in the study in order to have at least 112 patients (56 in each treatment group) completed and evaluable for efficacy. The study was stopped when a total of 129 patients were enrolled, because pathology disappeared (Summertime).

	Pholcodine		Dextromethorphan	
Evaluation Groups	*N*	*%*	*N*	*%*
Randomized	62	100.0	67	100.0
Safety set	62	100.0	66	98.5
Intent-to-treat	62	100.0	64	95.5
Per-protocol	59	95.2	60	89.6

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Gender (safety set)	*N*	*%*	*N*	*%*
Males	33	53.2	29	43.9
Females	29	46.8	37	56.1
Age (safety set)	*N*	*SD*	*N*	*SD*
	45.7	±13.6	47.9	±14.1

Diagnosis and main criteria for inclusions

Diagnosis. Acute non-productive cough with a frequency of daytime cough score ≥ 3 (on a 5-point scale) at baseline.

Inclusion criteria. Male or female patients aged from 18 to 70 years.

Exclusion criteria. Female pregnant, lactating or of child-bearing potential, not using a contraceptive method. Hypersensitivity to ingredients of pholcodine or DXM syrup, hepatic or renal disease, type I/II diabetes mellitus, heart failure (NYHA II/IV), neurological diseases. Respiratory failure, bronchial hypersecretion, neoplasm, lower respiratory tract diseases, tuberculosis and asthma. Cough for >2 weeks before inclusion. Antitussives, mucoactives, antidepressants, hypnotic or sedative drugs, β_2-agonists, ACE inhibitors, anthistaminics, antibiotics or oral corticosteroids, <2 weeks before inclusion.

Test product, dose and mode of administration, batch number

	Pholcodine (test product)	Dextromethorphan (comparator)
Dosage	19.65 mg, three time per day	19.95 mg, three times per day
Duration of the therapy	Three days (9 doses)	Three days (9 doses)
Mode of administration	Oral (15 ml of 0.131% syrup)	Oral (15 ml of 0.133% syrup)
Batch number	239CLI, expiry March 2006	3226GG21, expiry July 2005

The drugs were to be administered t.i.d. at the same time points (at awakening, after lunch and in the evening) by a measured cup of 15 ml provided in the packaging. No additional dose was allowed.

Statistical methods

This is a non-inferiority study. Sample size was calculated assuming that about 70% of the patients in each group improve their score by at least one point (corresponding to a 1 point decrease in the original five point rating scale). According to this background, it has been calculated that a minimum sample size of 56 patients in each group provides 90% power.

Efficacy analyses were primarily based on the ITT population (all randomized patients who received any study medication and with at least one assessment of daytime cough frequency). The demographic and baseline characteristics were assessed using appropriate methods, including Student-t-test or Wilcoxon-Mann-Whitney non parametric test for continuous variables, and Chi Square test or Fisher Exact test for categorical variables.

Primary analysis was performed on the ITT population and then on the PP population. A logistic regression for proportional odds was performed on change scores, including the treatment and center effect and the baseline score as covariate. The 95% CI of the odds ratio for treatment (pholcodine vs DXM) to improve was calculated and compared with the non-inferiority limit of 0.66. The logistic regression for proportional odds was also applied for the cough intensity and the change in night trouble.

No change to the planned analyses was performed after breaking the code

SUMMARY

Efficacy results

Primary analysis

The primary efficacy analysis of both the ITT and PP populations shows the non-inferiority of pholcodine compared to DXM in the daytime cough frequency reduction.

At day 3, the change from baseline of the mean daytime cough frequency in the ITT populations was -1.4 points (±0.9) for pholcodine and -1.3 (±0.8) for DXM, whereas at LOCF the changes were -1.3 points (±0.9) and -1.3 (±0.8) for pholcodine and DXM respectively (OR: 1.44; 95% CI: 0.73-2.82).

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The PP analysis confirms these results, as the lower bounds of the OR confidence interval at day 3 were 0.79 and 0.88, respectively for one-sided 95% and 90% CIs.

Both treatments were associated to an improvement in the daytime cough frequency of about 0.4 points per day, that was nearly linear over a period of three days.

Secondary analyses

The change from baseline in the daytime cough frequency at Day 1 and 2 showed in the logistic regression for proportional odds an odds ratio of 1.26 (95% CI lower bound: 0.61; 90% CI lower bound: 0.68) for day 1 and 0.92 (95% CI lower bound: 0.52; 90% CI lower bound: 0.58) for day 2. Results are similar when considering the PP set .

The percentage of patients who decreased their daytime cough frequency score of at least 2 points, at the end of the study was 43.5% and 37.5% respectively in the pholcodine and in DXM group. Logistic regression resulted, on the ITT set, in an odds ratio of 1.62 with a 95% CI lower bound of 0.72. Compared to non inferiority limit of 0.66 defined in the protocol, pholcodine can be considered as non-inferior to DXM for this endpoint at the 0.025 level and results are confirmed on the PP set .

Considering the percentage of patients who recovered at the end of the study, the logistic regression on the ITT set resulted in an odds ratio of 1.58 with a 95% CI lower bound of 0.66, paired to non-inferiority limit defined in the protocol; when performed on the PP set, the analysis gave an odds ratio of 1.59 with a 95% CI lower bound of 0.68. Also for this endpoint, pholcodine can be considered as non-inferior to DXM at the 0.025 level.

Also the overall response of night trouble performed on the ITT set confirmed the non-inferiority of pholcodine compared to DXM at the end of study, The logistic regression for proportional odds, performed on the ITT set resulted in an odds ratio of 1.46, in favour of pholcodine: the lower bounds of the OR confidence interval were 0.74 and 0.83, respectively for one-sided 95% and 90% CIs. Compared to the non-inferiority limit of 0.66, pholcodine can be considered non-inferior to DXM.

The mean cough intensity, the global efficacy and tolerability according to the patient and to the investigator failed to reject the null hypothesis.

No bias in the selection of the population was found being demography and baseline characteristics equally balanced in the two groups.

Safety results

Six of the 62 patients (9.7%) treated with pholcodine referred 8 AEs, 4 of which (6.5%) were considered definitively, probably or possibly related to the treatment. One patient was permanently discontinued for emergent epigastralgia.
In the DXM group 11 of the 66 patients (16.7%) referred 19 AEs, 11 of which (10.6%) were considered definitively, probably or possibly related to the treatment. Three patients were permanently discontinued for five emergent AEs (vomiting and vasovagal syncope, nausea and vomiting, asthenia and somnolence).

In this study both pholcodine and DXM demonstrated to be safe as antitussive agents for treatments of 3-day duration. The two drugs have similar safety profile in body system distribution of AE, being gastrointestinal disorders the most frequently observed (nausea, vomiting and epigastralgia), in severity (only mild or moderate) and outcome as AEs resolve in few days and do not require treatment. No serious AE was reported.

By the way, it can be noticed that patients receiving pholcodine had a lower rate of related AEs. However due to the relatively small number of AEs observed is not possible to reach a definitive conclusion, even if the overall safety findings suggest that pholcodine might have a better safety and tolerability profile than DXM.

According to the investigator's assessment in double-blind conditions, the global tolerability of pholcodine was considered significantly better than DXM.

Conclusions

In the Western World DXM is one of the most widely used antitussive ingredient in both prescribing and over-the-counter medications and its efficacy in acute cough after treatments of brief duration has been proved in well-conducted placebo

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controlled clinical trials .

The primary objective of this study was to demonstrate that efficacy on daytime cough frequency of pholcodine was non-inferior to that of DXM. After three days of treatment, the primary efficacy analysis (change from baseline of the mean daytime cough frequency) of both the ITT and PP populations shows the non-inferiority of pholcodine compared to DXM.

At the end of the study, also the decrease in daytime cough frequency score of at least 2 points, the percentage of patients who recovered from illness and the overall response of night trouble confirmed the non-inferiority of pholcodine compared to DXM, whereas the mean cough intensity, the global efficacy and tolerability according to the patient and the global efficacy according to the investigator failed to reject the null hypothesis.

In this study both pholcodine and DXM showed a very good safety profile as antitussive agents in a 3-day treatments,

The two drugs have similar safety profile in body system distribution of AE, being gastrointestinal disorders the most frequently observed (nausea, vomiting and epigastralgia). No serious AE was reported.

However, as far as the overall incidence of related AEs is concerned, pholcodine showed a lower rate and a better safety and tolerability profile than DXM, supported the investigator's assessment of the global tolerability that was significantly better in the pholcodine than in the DXM group.

Date of the report

1 December 2005